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LEUKÆMIA IN BENZENE WORKERS

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Summary Workers occupationally exposed to benzene in 1940–49 were followed for vital status up to 1975. In comparison with two control populations, a significant ($P<0.002$) excess of leukæmia was observed. A five-fold excessive risk of all leukæmias and a ten-fold excess of deaths from myeloid and monocytic leukæmias combined are demonstrated in the study population compared with controls. These figures underestimate the true leukæmia risk to benzene-exposed workers, because follow-up is only 75% complete and the untraced 25% of the study population were all regarded, in the statistical analysis, as being alive at the end of the study period.

The environment of the workers in the study population was not contaminated with solvents other than benzene, and existing records indicate that the benzene levels themselves were generally below the limits recommended at the time of their measurement.

INTRODUCTION

ONE of the earliest reports of benzene-related blood disorders consistent with what is now known to result from benzene poisoning was published in Paris in 1897.[1] In 1928, a clearly established case of leukæmia was associated with benzene exposure in Italy.[2] Since then, many cases of leukæmia associated with exposure to benzene have been reported from various parts of the world.[3-9] A significant excess of chromosomal aberrations has also been observed in benzene-exposed workers.[10]

Ishimaru et al.[6] demonstrated a significant association between leukæmia and occupations with probable exposure to benzene, and Aksoy et al.[7] reported a significantly greater incidence of leukæmia in shoe workers exposed to benzene than in the general population. In

1976 Vigliani[4] reported that 150 cases of leukæmia attributed to benzene had been identified in Italy. McMichael et al.[11] demonstrated an excess of leukæmia among rubber workers previously exposed to solvents, including benzene. However, in that study the leukæmogenic effect could not be attributed directly to benzene because of concomitant exposure to other solvents used in the manufacture of rubber products.

Before the 1914–18 war, benzene was used mainly as a solvent in the rubber industry, but during the war the demand for toluene in the manufacture of explosives greatly stimulated benzene production. Currently, 87% of benzene is used as a raw material in the synthesis of compounds such as styrene, phenol, and cyclohexane. Approximately 10·2 billion lb (4·6 billion kg) were produced in the U.S. in 1973, 3·5 billion lb (1·6 billion kg) in Japan in 1972, and 1·2 billion lb (0·5 billion kg) in the U.K. in 1972.[12] In the 50 years since the first reported case of benzene-associated leukæmia, benzene has been neither widely acknowledged nor uniformly controlled as a carcinogen in the U.S.[13] The failure to control benzene as a carcinogen has resulted primarily from the reluctance of industry and Government to accept the accumulated case-reports and epidemiological observations as scientific evidence of the leukæmogenic properties of benzene. Today, in the U.S. alone, an estimated two million workers are at risk of exposure to benzene.[14] For these reasons we have studied mortality patterns in workers occupationally exposed to benzene in the production of a natural rubber cast film (rubber hydrochloride, marketed under the trade name 'Pliofilm') at two localities in Ohio.

INDUSTRIAL-HYGIENE ASSESSMENT

Production Methods

In the production of 'Pliofilm', natural rubber was masticated in an internal mixer, passed through a mill, and conveyed to mixing-tanks, where benzene was added and the mixture was agitated. The resulting solution was pumped to a blending-tank, then transferred into a reactor vessel, where it was treated with hydrochloric acid to form rubber hydrochloride. At this stage, more benzene was added to adjust the proportion of solids in the solution. The rubber hydrochloride was transferred to a neutralising-tank, where pliofilm scraps, soda ash, steam, plasticisers, and more benzene were added. After filtration, the rubber hydrochloride solution was pumped to a casting-unit, then it was spread on a continuous conveyor,

where the benzene was evaporated, and the finished film was taken up on a roll. The gas containing benzene was exhausted from the casting-unit, passed through a wet scrubber, and channelled into an activated-charcoal absorber unit, where benzene was recovered and recycled. The rolls of pliofilm were transferred to another room, where they were inspected, trimmed, cut to customer specification, and packed (primarily for food wrapping). In the production of pliofilm, the only material known to be associated with blood disorders was benzene. Other materials used included hydrochloric acid, soda ash, and small amounts of antioxidants and plasticisers. The manufacturing process was essentially identical at both Ohio localities.

Environmental Monitoring

In 1942, Wilson, as a former member of corporate management, recommended a policy for the rubber industry, which would include pliofilm operations, of periodic air monitoring and a complete blood-count for all new employees.[15] It was his view that "a closed system of ventilation where the workman comes in contact with no fumes is ideal. Any other type of ventilation is not entirely safe." Shortly thereafter, extensive exhaust ventilation equipment was installed in the pliofilm department in one locality. The Industrial Commission of Ohio, after surveying that department in 1946, reported that, "Tests were made with benzol detectors and the results indicate that concentrations have been reduced to a safe level and in most instances range from zero to 10 or 15 parts per million".[16] A further investigation of benzene exposure in that department in 1956 concluded that exhaust ventilation controls were of excellent design.[17] In the early 1960s benzene point-source concentrations were measured by company personnel using detector tubes. A total of 112 surveys were conducted in the period 1963–74. These and earlier surveys have indicated that employees' benzene exposure was generally below the recommended limit in effect at the time of each survey[12,14,18-20] (table I).

TABLE I—CHRONOLOGY OF RECOMMENDED BENZENE CONCENTRATIONS IN WORKPLACES IN U.S.A.

Year	Concentration (p.p.m.)	Reference
1941	100 M.A.C.	16, 17
1947	50 8h T.W.A.	14
1948	35 8h T.W.A.	14
1957	25 8h T.W.A.	14
1963	25 Ceiling	14
1969	10 8h T.W.A.	18
1971	10 8h T.W.A.	13

M.A.C.=Maximum allowable concentration.
T.W.A.=Time-weighted average.

Historical environmental data for the second locality in Ohio is less well defined. However, our own observations, discussions with company personnel, and the meagre environmental data that have been retained suggest that employees' benzene exposure at this location was generally well within the recommended limits.

RETROSPECTIVE COHORT STUDY

Methods

All White men who had had direct exposure to benzene at any time beween Jan. 1, 1940, and Dec. 31, 1949, were studied. The departments and jobs involving direct exposure to benzene were determined by a survey by N.I.O.S.H. personnel, which included a review of the pliofilm process, engineering controls, and air-sampling data. Company personnel also assisted in these determinations. Job classifications involving benzene exposure were determined without knowledge of the workers' vital status.

Follow-up of all study-cohort members was attempted for the time period from first employment to June 30, 1975. To date, vital status has been determined for approximately 75% of the 748 cohort members. The remaining 25% were assumed to be alive to avoid overestimating the true risk of lymphatic and hæmopoietic malignancies associated with benzene exposure. Causes of death were determined from death certificates and were coded according to the International Classification of Diseases in effect at the time of death; these codes were then converted to I.C.D. 7th revision numbers. A modified life-table technique was used to generate person-years at risk of dying according to 5-year age-group and 5-year calendar periods.

Person-years of observation and causes of death were determined for the period Jan. 1, 1950, to June 30, 1975. Person-years of observation and deaths occurring before Jan. 1, 1950, were excluded from analysis since vital statistics on lymphatic and hæmopoietic malignancies were not published before that date.

Two populations were chosen as control groups for generating the numbers of expected deaths in the study population. The first group consisted of the U.S. White male general population standardised for age and time period over which the study cohort lived. The second group consisted of 1447 White men who had been employed in Ohio at a fibrous-glass construction-products factory between Jan. 1, 1940, and Dec. 31, 1949,

and who had achieved 5 or more years of employment by June 1, 1972 (which was the cut-off date for vital-status ascertainment in the fibrous-glass control population).[21]

Results

There were 140 observed deaths from all causes among benzene-exposed workers compared with 187·6 expected deaths (table II). This deficit reflects in part the incomplete follow-up of the study population. There was a significant excess of deaths from malignancy of the lymphatic and hæmopoiëtic systems (I.C.D. 200–205) compared to that expected on the basis of death-rates of U.S. White males. This is due almost entirely to an excess of leukæmia deaths (I.C.D. 204). To date, 7 leukæmia deaths have been observed, compared with an expected 1·38 ($P<0·002$) based on rates for U.S. White males and an expected 1·48 ($P<0·002$) based on rates for fibrous-glass workers. Even more striking is the observation that all 7 leukæmia deaths were from either the myelogenous or monocytic type. Data for cell type, age at death, and interval since initial exposure to benzene are shown in table III. The period between initial exposure and death ranged from 2 to 21 years. These observations, indicating a specific type of leukæmia, are consistent with the data of Vigliani,[4] which show a predominance of acute myelogenous leukæmia among workers exposed to benzene in the rotogravure and shoe-manufacturing industries in Italy. Since data for specific types of leukæmia mortality in the U.S. are not readily available for the study period, incidences for myeloid, monocytic, and total leukæmia from the Connecticut Tumor Registry[22] for the period 1960–62 were applied to the age-distribution of the benzene-exposed cohort to generate the specific proportion of total-leukæmia cases which would be of the myelomonocytic types. Of the total expected number of incidence cases of leukæmia, 50·37% were calculated to be of the myelogenous and monocytic types. This proportion was applied to the total number of expected leukæmia deaths in the study cohort which had been previously generated on the basis of rates for the U.S. White male population. The results indicated an expected 0·6967 (0·5037 × 1·3831 = 0·6967) deaths from myelogenous and monocytic leukæmia, compared with 7 observed, the standardised mortality-ratio being 1004. Thus, pliofilm workers exposed to benzene have an estimated 10-fold risk of dying from

TABLE II—STATUS ON APRIL 13, 1977, OF OBSERVED DEATHS FROM SPECIFIC CAUSES AMONG WHITE MALES BETWEEN JAN. 1, 1940, AND JUNE 30, 1975, WHO WERE EXPOSED TO BENZENE AND EMPLOYED SOMETIME BETWEEN JAN. 1, 1940, AND DEC. 31, 1949, AS CONTRASTED WITH EXPECTED DEATHS BASED ON BOTH THE U.S. WHITE-MALE POPULATION (U.S.W.M.) AND AN INDUSTRIAL POPULATION EXPOSED TO FIBROUS GLASS (F.G.).

Causes of death (I.C.D. codes)*	Benzene-exposed workers			
	Deaths observed	Deaths expected	Comparison group	S.M.R.
All causes	140	187·5809	(U.S.W.M.)	075
(200–205)	9	3·4497	(U.S.W.M.)	260†
(204)	7	1·3831	(U.S.W.M.)	506‡
(200–205)	9	5·1020	(F.G.)	176
(204)	7	1·4758	(F.G.)	474‡

*I.C.D. 7th Revision Codes. (200–205) = Total lymphatic and hæmopoietic cancer. (204) = Leukæmia only.
†$P<0.05$
‡$P<0.002$
S.M.R. = observed/expected × 100

TABLE III—CASES OF LEUKÆMIA IDENTIFIED BY APRIL, 1977, AMONG WORKERS EXPOSED TO BENZENE BETWEEN 1940 AND 1949 DURING PLIOFILM MANUFACTURE

Case no.	Type of leukæmia	Age at death (yr)	Period from initial exposure to death (yr)
1	Acute myelogenous	60	13
2	Acute myelogenous	65	10
3	Acute myelogenous	62	21
4	Acute myelogenous	57	19
5	Monocytic	57	15
6	Chronic myelogenous	29	2
7	Monocytic	36	17
8*	Myelogenous	28	3

*Indicates leukæmia case which did not fit into cohort definition. The subject began employment in 1950.

myelogenous and monocytic leukæmia.

As a result of past failure to control benzene as a carcinogen, millions of people, without knowledge of the hæmopoietic dangers, are continually being exposed to benzene at work. In addition, unknown numbers of consumers, including children, are exposed to benzene at home, from sources such as model-aeroplane glue and paint strippers (some containing up to 50% benzene).

We hope that our findings, which demonstrate overwhelmingly an increased risk of leukæmia in workers exposed to benzene, will stimulate efforts to control occupational and consumer exposure to benzene, an agent known for almost a century to be a powerful bone-marrow poison.[1]

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